UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,766	07/12/2001	Avi Ashkenazi	10466/70	4054

30313 7590 09/27/2002

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,766	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2001 and 27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendments, filed 7/12/01 and 8/27/02 (Paper Nos. 9 and 10), are acknowledged.
Claims 1-38 have been canceled.
Claims 39-51 have been added.
Claims 39-51 *are pending.*

Sequence Compliance

2. Sequence compliance: The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

Drawings

3. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

Oath

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: non-initialed and non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

See in particular the residence information for Wei-Qiang Gao.

Priority

5. According to the priority statement filed 8/27/02, priority for the instant application is claimed to USSN 09/665,350 (9/18/00), which is a CON of PCT/US00/04414 (2/22/00), which is a CIP of PCT/US00/03565 (2/11/00) which is a CIP of PCT/US98/19330 (9/16/98) which claims priority to provisional application 60/063,045 (10/24/97).

A) Based on the information given by applicant and an inspection of the patent applications, the examiner has concluded that the subject matter defined in this application is supported by the disclosure in USSN 09/904,766, filed 7/12/01, but is not supported by any of the others because the instant subject matter lacks the necessary support under 35 USC 112, first paragraph, as set forth below. Accordingly, the subject matter defined in claims 39-51 appears to have an effective filing date of 7/12/01.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 7/12/01 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to 7/12/01.

B) In addition, the application claims benefit to the international applications identified supra. Applications that are filed on or after November 29, 2000, and that claim benefit to an earlier-filed international application *must include in the first sentence of the specification an indication of whether the international application was published in English under PCT Article 21(2)* (regardless of whether the benefit for such application is claimed in an application data sheet). See 37 CFR 1.78(a)(2). The indication, as required by 37 CFR 1.78(a)(2), is missing. Applicant must supply the missing indication as an amendment to the specification in the reply to this Office action.

C) Finally, Applicant is reminded that the status of nonprovisional parent application(s) (whether patented or abandoned) should also be included in the priority claim If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

IDS

6. The information disclosure statement filed 3/22/02 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because:
the sequence alignments provided fail to provide any of the relevant information with respect to publisher, author (if any), title, relevant pages of the publication, date, and place of publication with respect to the sequences compared.

Title

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

The following new Title is suggested: PRO269 POLYPEPTIDES

Specification

8. The disclosure is objected to because it contains an embedded hyperlink. See for example page 71, line 28. Applicant is required to delete the embedded hyperlink. See MPEP § 608.01.

Applicant is requested to carefully review the specification for any additional hyperlinks or other forms of browser executable code and delete them.

9. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

Applicant is requested to update the location of the ATCC disclosed on page 250 to reflect the ATCC's current address:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

Claim Rejections - 35 USC § 101

10. 35 U.S.C. § 101 reads as follows:

> *"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".*

11. Claims 39-51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

Asserted Utility based on homology to thrombomodulin:

The instant specification discloses that the PRO269 polypeptide of SEQ ID NO:96 has "significant" homology to urinary thrombomodulin and various thrombomodulin analogues (e.g., specification page 103, lines 4-13).

The specification on page 12 at line 30 to page 13 at line 1 discloses that thrombomodulin is a natural anticoagulant that has a possible therapeutic use an antithrombotic agent with reduced risk for hemorrhage as compared with heparin.

Based upon the homology of PRO269 to thrombomodulin, the specification asserts that PRO269 is a new member of the thrombomodulin family (e.g., specification page 103, lines 4-13). The specification further asserts that PRO269, like thrombomodulin, may also be useful as an antithrombotic agent with reduced risk for hemorrhage as compared with heparin (e.g., page 132 at line 38 to page 133 at line 3).

In the instant case, Applicant does not provide an alignment of either the DNA or protein sequences to the DNA or protein sequence of thrombomodulin. Alignment of the PRO269 protein (SEQ ID NO:96) over its full length (i.e., residues 1-490) to human thrombomodulin provides a query match of only 8.7%, with a best local similarity of 25.7% over residues 16-286 (see attached alignment "A"). Alignment of the extracellular domain of PRO269 (i.e. residues 17-398) provides a query match of 10.9% with a best local similarity of 25.5% over residues corresponding to 19-289 of the full length of SEQ ID NO:96 (see attached alignment "B").

However, other proteins not related to thrombomodulin in function also share a level of homology to PRO269 similar to that shared by PRO269 and thrombomodulin. For example, Tenner et al. (U.S. Pat. No. 5,965,439) teach the cell surface protein C1qRp (SEQ ID NO:2 of Tenner et al.). Alignment of PRO269 (instant SEQ ID NO:96) and C1qRp (SEQ ID NO:2 of Tenner et al.) produces a query match of 11.8% and a best local similarity of 21.4% over residues 1-451 of instant SEQ ID NO:96 (see attached alignment "C"). C1qRp is taught by Tenner et al. to function in host defense by functioning as the receptor for the complement component C1q (see entire document, e.g., columns 1-2 "Introduction" and "Summary of the Invention"). Tenner et al. also note at column 35, lines 55-60 that diverse, non-related extracellular proteins show some homology to one another due to the sharing of EGF domains. The presence of an EGF domain in the PRO269 polypeptide thus explains the low level of homology to both thrombomodulin and C1qRp.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306).

Thus the homology of PRO269 to thrombomodulin is so low and indistinct compared to other proteins having diverse functions that the ordinary artisan cannot consider it more likely than not that PRO269 is a member of the thrombomodulin family, or that PRO269 has the same function as thrombomodulin based upon the homology of the PRO269 polypeptide to thrombomodulin. The presence of an EGF domain in both PRO269 and thrombomodulin is sufficient to explain the homology results; but as suggested by Bork et al. supra, the sharing of a small domain does not establish that this new protein shares any function with thrombomodulin.

Thus, the specification fails to support the asserted specific and substantial utility of use of the PRO269 polypeptide as an antithrombotic agent with reduced risk for hemorrhage as compared with heparin.

Asserted Utility based upon "positive" results in certain disclosed assays:

First, it is noted that there is no well-established utility for the PRO269 polypeptide on record or of which the Examiner is aware.

The specification on pages 208-209 discloses that PRO269 tested positive for stimulation of a mixed lymphocyte reaction (assay 24), and asserts that any polypeptide positive in this assay can be used for the enhancement of an immune response.

The specification on page 214 discloses that PRO269 tested positive for the ability to inhibit adult heart hypertrophy in an in vitro assay (assay 42), and asserts that PRO269 can be used to treat cardiac disorders associated with cardiac hypertrophy.

The specification discloses on pages 216-217 that PRO269 can induce c-fos in cortical neurons in an in vitro (assay 83), and asserts that any polypeptide with this activity could be used to treat nervous system disorders where neuronal proliferation would be beneficial.

The specification on page 217 discloses that PRO269 either affected glucose and/or FFA uptake in an in vitro assay (assay 106), and asserts that any polypeptide with this activity would be useful for treating any disorder where stimulation or inhibition of glucose uptake by skeletal muscle would be beneficial.

The specification on pages 222-235 also discloses that PRO269 is expressed in certain tumors, and asserts that antibodies to any polypeptide expressed in certain tumors would be useful in tumor therapy (page 234, lines 1-3).

Thus the specification discloses that the polypeptide PRO269 is associated with several testable in vitro functions. However, while the utilities asserted to be associated with each assay in which PRO269 is positive appear to be specific and substantial; it is not credible based upon the information of record that a positive reaction in the disclosed assays provides sufficient support such that the skilled artisan would consider it more likely than not that the PRO269 polypeptide would in fact have the utility asserted with respect to any one or more of the assays in which PRO269 is positive.

The skilled artisan would not view the asserted utilities as credible because there is no indication of the degree of the stimulation or suppression disclosed in the assays in which PRO269 is positive. For example, in assay 24 in which PRO269 "stimulates" and MLR, the specification discloses at page 209, lines 17-18 that *any* value greater than control indicates a stimulatory effect for the test protein. However, without some indication of the extent of stimulation (i.e., how does the stimulation induced by PRO269 compare to that of the positive control) and the relevance of the positive control (i.e., does the positive control have the asserted utility); the skilled artisan would not find it more likely than not that PRO269 would have the associated asserted utility of being able to enhance an immune response. Thus in the absence of objective evidence with respect to the degree of activity relative to both negative and positive controls and the relevance of the positive control to the asserted utility, the instant assays do not appear to provide sufficient support as to the credibility of the associated asserted utilities.

Applicant is invited to make of record objective evidence supporting the credibility of the asserted utilities.

However, at present the instant disclosure fails to clearly establish how one of skill in the art could use the claimed invention in a way that constitutes a credible specific and substantial utility. The disclosed functions appear only to provide starting points for further research and investigation into potential practical uses of the claimed PRO269 polypeptide. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ 689 (1966) at 696.

Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 39-51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

14. The PRO269 polypeptide of SEQ ID NO:96 itself does not appear to be enabled for the reasons set forth supra. However, even were sufficient objective evidence provided that the PRO269 polypeptide of SEQ ID NO:96 were enabled for one or more of the asserted uses, the following rejections would still apply:

A) Claims 39-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification asserts that the PRO269 polypeptide of SEQ ID NO:96 can be used:

i) as an antithrombotic agent with reduced risk for hemorrhage as compared with heparin (e.g., page 132 at line 38 to page 133 at line 3);
ii) to enhance an immune response (e.g., page 208 at lines 29-30);
iii) to treat cardiac disorders associated with cardiac hypertrophy (e.g., page 214 at lines 6-8);
iv) to treat nervous system disorders where neuronal proliferation would be beneficial (e.g., page 216 at lines 31-32);
v) to treat any disorder where stimulation or inhibition of glucose uptake by skeletal muscle would be beneficial (e.g., page 217 at lines 20-22); and
vi) to provide antibodies that would be useful in tumor therapy (page 234, lines 1-3).

These asserted uses are drawn to several conditions that appear to be unrelated. The specification does not provide working examples with respect to any of these asserted uses.

Each asserted use of the PRO269 polypeptide is based upon a disclosed positive reaction in a particular screening assay. As noted supra, the skilled artisan would not consider these asserted uses of the PRO269 polypeptide to be credible based upon the instant disclosure. However, even were the skilled artisan to consider it more likely than not that the PRO269 polypeptide could be used in any one or more of the asserted utilities, it would still require extensive and undue experimentation of the skilled artisan to actually use the PRO269 polypeptide as disclosed.

First, it is noted that the PRO269 polypeptide has not been shown to have any function *in vivo*. The *in vivo* application of an uncharacterized protein is fraught with technical difficulties. Pharmaceutical therapies in the absence of *in vivo* data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Anti-thrombotic:
The asserted use of the PRO269 polypeptide as an anti-thrombotic is based upon a low level of homology of PRO269 to the anti-thrombotic thrombomodulin (see e.g., pages 132-133). As discussed in detail supra, the state of the art did not recognize that the low level of homology of PRO269 to thrombomodulin was sufficient to suggest that the ordinary artisan would consider it more likely than not that PRO269 shared functionality with thrombomodulin (please see supra for supporting evidence regarding the lack of predictability of protein function based on homology). Applicant provides no working examples with respect to any activity recognized by the state of the art to be predictive of anti-thrombotic activity (e.g., binding of thrombin or activation of Protein C, see Esmon's review of thrombomodulin's activity in The FASEB J. 1995; 9:946-955). Thus it is highly unpredictable that a molecule with only very limited homology to thrombomodulin and no demonstrated activity that is consistent with an anti-thrombotic function could in fact be used as an anti-thrombotic. As noted supra, the application of PRO269 to in vivo therapies is also highly unpredictable. Clearly, extensive and undue experimentation would be required of the skilled artisan to use the PRO269 polypeptide as an anti-thrombotic agent.

Immune response stimulator:
The asserted use of the PRO269 polypeptide as an immune response stimulator is based upon its activity in a mixed lymphocyte reaction (see Example 74, pages 208-209). However, the specification does not appear to provide sufficient guidance as to the conditions for which stimulation of an immune response would be desirable. Neither does the specification provide sufficient guidance as to how the immune response stimulation is to be accomplished. The specification does not demonstrate that PRO269 can directly stimulate lymphocytes (i.e., function by itself to stimulate lymphocytes). In the context of the in vitro mixed lymphocyte reaction, PRO269 does not provide the only stimulatory signal; rather the art recognized that the primary stimulatory signal is provided by irradiated "stimulator" cells. Neither does the specification appear to provide guidance as to how the "stimulatory" signal provided by the irradiated stimulator cells in the mixed lymphocyte reaction can be provided in vivo. In conjunction with the uncertainties noted above with respect to in vivo use of the PRO269 polypeptide and the lack of guidance as to the conditions for which immune stimulation would be desirable, it appears that extensive and undue experimentation would be required of the skilled artisan to use the PRO269 polypeptide as a stimulator of immune responses.

Treatment of cardiac disorders associated with cardiac hypertrophy:
The asserted use of the PRO269 polypeptide for treatment of disorders associated with cardiac hypertrophy is based upon its ability to inhibit adult heart hypertrophy in an in vitro assay utilizing isolated myocytes (see Example 83, page 214). However, the record does not establish that this in vitro assay without further characterization in one or more in vivo assay is reasonably predictive that a protein can be used to treat cardiac disorders associated with cardiac hypertrophy. For example, the art teaches the use of the in vitro assay in conjunction with in vivo assays of cardiac hypertrophy and notes that it is the in vivo assays that provide valuable information about the therapeutic potential of a new agent (see for example Jin et al. in U.S. Patent No. 6,187,304, entire document but especially the discussion of assays at columns 10-11 and the comment regarding the value of the in vivo assay at column 11, lines 17-19). Jin et al. also note that most treatments of cardiac hypertrophy are applicable only to certain indications that are determined by the underlying cardiac disease (see e.g., column 3 at line 66 to column 4 at line 59). In conjunction with the uncertainties noted above with respect to in vivo use of the PRO269 polypeptide, it appears that further undue experimentation would be required of the skilled artisan to use the PRO269 polypeptide to treat cardiac hypertrophy, particularly without guidance as to one or more underlying cardiac diseases. *It is also noted that PRO269 was not disclosed to be positive in what appears to be a related assay of inhibition of neonatal (rather than adult) heart hypertrophy (Example 100, page 237).*

Treatment of nervous system disorders where neuronal proliferation would be beneficial:
The asserted use of the PRO269 polypeptide for treatment of nervous system disorders where neuronal proliferation would be beneficial is based upon the ability of PRO269 to induce c-fos in cortical neurons in vitro (see Example 87, pages 216-217). However, the record does not establish that this in vitro assay is predictive of the ability to treat any nervous system disorder. Besides the general art-recognized difficulties associated with treatment of nervous system disorders in general, Herdegen et al. (Oncogene 2001; 20:2424-2437) review that the role of c-fos, the protein disclosed to be induced by PRO269, is far from clear and that c-fos, although promiscuously expressed following a variety of stimuli, is often associated with neurodegenerative events (see entire document, but especially the comments on page2425 "c-fos", page 2430 "c-fos/ERK-axis" and page 2432 "The promiscuous expression of the c-fos protein..."). Thus the disclosure that PRO269 induces c-fos in cortical neurons does not appear to be consistent with therapeutic treatment of nervous system disorders where neuronal proliferation would be beneficial, since there is evidence that c-fos is associated with neurodegenerative events. Given the uncertain role of c-fos and the uncertainties noted above with respect to in vivo administration of PRO269, it appears that further undue experimentation would be required of the skilled artisan to use the PRO269 polypeptide to treat nervous system disorders where neuronal proliferation would be beneficial.

Treatment of disorders where stimulation or inhibition of glucose/FFA uptake would be beneficial:
The asserted use of the PRO269 polypeptide for treatment of any disorder where stimulation or inhibition of glucose/FFA uptake by skeletal muscle would be beneficial is based upon the ability of PRO269 to have some effect (either stimulatory or inhibitory) on glucose and/or FFA uptake by skeletal muscle in response to insulin in vitro (see Example 89, page 217). Given that the disclosure does not indicate whether the effect of the PRO269 polypeptide is stimulatory or inhibitory, the skilled artisan has not been given sufficient guidance as to which disorders to treat by administering PRO269. Even were the nature of the effect disclosed, the specification also does not appear to establish that the in vitro assay is predictive of the ability to treat any particular disorder associated with stimulation or inhibition of glucose and/or FFA uptake. Combined with the uncertainties noted above with respect to in vivo administration of PRO269, it appears that further undue experimentation would be required of the skilled artisan to use the PRO269 polypeptide to treat any disorder where stimulation or inhibition of glucose uptake by skeletal muscle would be beneficial.

Tumor therapy:
The asserted use of the PRO269 polypeptide for tumor therapy is based on the preparation of antibodies to PRO269 and their use as antagonists of the PRO269 polypeptide (see e.g., page 235, lines 1-3 in view of the DNA amplification results on pages 222-234). However, given the results on page 230-234, there does not appear to be a particular tumor type that is associated with PRO269. Neither does the specification appear to provide sufficient guidance as to how the skilled artisan would use an antibody antagonist to PRO269. Even were PRO269 an established target on tumors or a subclass of tumors, the art recognized that it was unpredictable that unconjugated antibodies could be used as a tumor therapeutic (e.g., see Dillman in J. Clin. Oncol. 1994; 12:1497-1515). Without additional guidance with respect to PRO269 in particular and the use of antibody antagonists, it would require undue experimentation of the skilled artisan to utilize an antibody to PRO269 for tumor therapy.

B) Claims 39-43 and 50-51 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, *even were it shown to be enabling* for the PRO269 polypeptide of SEQ ID NO:96, *still would* not reasonably provide enablement for polypeptides having less than 100% identity to at least the extracellular domain of SEQ ID NO:96. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a polypeptide having at least 80, 85, 90, 95 or 99% amino acid sequence identity to the PRO269 polypeptide of SEQ ID NO:96 or the extracellular domain thereof, either with or without the leader sequence. There is no functional limitation in the claims. Applicants have taught a single embodiment, the PRO269 polypeptide encoded by the cDNA deposited under ATCC accession number 209397.

There are three assayable activities disclosed in the specification for the polypeptide of PRO269: stimulation of a mixed lymphocyte reaction (pages 208-209), inhibition of adult heart hypertrophy (page 214) and induction of c-fos in cortical neurons (page 216-217). Although the specification also discloses on page 217 that the PRO269 polypeptide has some effect on glucose and/or FFA uptake, the nature of the effect is not disclosed. However, the instant claims do not require the PRO269 polypeptide variants to share any testable function with PRO269. Neither does the specification appear to provide sufficient guidance as to which amino acids of PRO269 are essential to any of the functions ascribed to the PRO269 polypeptide. Such guidance requires knowledge as to which encoded amino acids actually contribute to particular functions versus which encoded amino acids are non-essential to those functions. The instant specification does not appear to provide this knowledge and guidance with respect to an assignment of function to specific amino acids.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the PRO269 polypeptide and still maintain the assayable activities disclosed are unpredictable; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

15. Claims 39-43 and 50-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *Written Description* rejection is set forth herein.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.
Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 370, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

16. Claims 39-44 and 49-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

It is apparent that the cDNA deposited under ATCC accession number 209397 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines which produce these antibodies. See 37 CFR 1.801-1.809.

It is noted that page 250-251 of the specification indicates that the relevant clone DNA38260-1180 was deposited with the ATCC on October 17, 1997 under the terms of the Budapest Treaty and that:

> "[t]he deposits will be made available by ATCC under terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent US patent...."

However, this agreement between Genentech Inc. and the ATCC does not appear to meet the requirements set forth in 37 CFR 1.808 (a)(2) and MPEP 2410-2410.01 which state that Applicant is required to assure that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Although Applicant has deposited lone DNA38260-1180 with the ATCC under the Budapest Treaty, there appears no assurances indicated above. Applicant's provision of these assurances would obviate this objection/rejection.

Applicant is also reminded to amend the specification to disclose current ATCC address:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

18. Claims 39-44, 48 and 50-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "the extracellular domain" ... "lacking its associated signal peptide" (for example claim 39(d)) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

35 U.S.C. § 102

19. The following rejections under 35 U.S.C. § 102 are made under the assumption that the effective filing date for the instantly claimed invention is 7/12/01, which is the actual filing date of the instant application.

Given the uncertainty associated with the effective filing date of the instant claims, certain rejections have been set forth in the alternative under more than one paragraph of 35 U.S.C. 102 until the effective filing date of the claims can be established.

Claim Rejections – 35 U.S.C. § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –

> *(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.*
>
> *(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

21. Claims 39-51 are rejected under 35 U.S.C. 102(b), *or in the alternative under 35 U.S.C. 102(a)*, as being anticipated by Wood et al. (WO 99/14328, see pages 1, 12, 39, 56, 72, 83-85, 92-98, 101, 108-112, 126-127, 185-187, Figures 35 and 36), as evidenced by the attached alignment "D".

Wood et al. teach an isolated PRO269 polypeptide having the amino acid sequence of SEQ ID NO:96 as shown in Figure 36. The PRO369 polypeptide has 100% amino acid sequence identity to the amino acid sequence of the PRO269 polypeptide shown in Figure 36 (SEQ ID NO:96) of the instant application, as evidenced by the attached alignment. Wood et al. teach also teach the isolated PRO269 extracellular domain (e.g., page 39, lines 34-35). Wood et al. further teach that the cDNA encoding the PRO269 polypeptide is contained within ATCC deposit number 209397 (page 186 at line 2 in view of page 56 a lines 16-19). Wood et al. teach expression of PRO269 in host cells, including eukaryotic host cells, and isolation of the expressed protein (pages 93-97); these expressed PRO269 polypeptides would inherently lack the signal peptide. It is noted that the comprising language of claim 48 reads on the full length molecule, which is a molecule comprising the extracellular domain. Finally, Wood et al. teach chimeric polypeptides in which PRO269 is fused to a heterologous polypeptide that is either an epitope tag or an Fc region of an immunoglobulin (see page 84 at lines 20-29).

The reference teachings thus anticipate the instant claimed invention.

22. Claims 39-46 and 49-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Valenzuela et al. (WO 00/11015, see pages 1-2, 115-118, 167-168, 171-176, 183-184, 207-209 and pages 68-70 of the sequence listing), as evidenced by the attached alignment "E".

Valenzuela et al. teach an isolated vp15_1 polypeptide having the amino acid sequence of SEQ ID NO:72 (see e.g., pages 68-70 of the sequence listing). The vp15_1 polypeptide has 100% amino acid sequence identity to the amino acid sequence of the polypeptide shown in Figure 36 (SEQ ID NO:96), as evidenced by the attached alignment, and therefore anticipates section (a) of instant claims 39-44 and claim 45. With respect to section (e) of the instant claims 39-44, as well as claim 49; the polypeptide encoded by the cDNA deposited under ATCC accession number 209397 is the same as the full length of instant SEQ ID NO:96, and is therefore also anticipated by the teachings of the vp15_1 polypeptide.

Valenzuela et al. also teach the mature vp15_1 protein at page 167, lines 10-12, lacking the associated signal peptide, and therefore anticipate section (b) of instant claims 39-44 and 46.

Valenzuela et al. also teach chimeric polypeptides in which the vp15_1 polypeptide is fused to a heterologous polypeptide that is a epitope tag (page 184, lines 25-34) and therefore anticipate instant claims 50-51.

The reference teachings thus anticipate the instant claimed invention.

Conclusion

23. No claims are allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
September 27, 2002

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
9/27/02